

**CAROL DAVILA UNIVERSITY OF
MEDICINE AND PHARMACY BUCHAREST**



**HABILITATION THESIS
ABSTRACT**

**INNOVATIVE THERAPEUTIC STRATEGIES
FOR OXIDATIVE STRESS- ASSOCIATED
DISEASES**

Associate Professor Marilena GÎLCĂ-VASILE, PhD

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The present habilitation thesis entitled *Innovative therapeutic strategies for oxidative stress-associated diseases* reviews the author's most important scientific, professional and academic results obtained subsequently to the PhD (2003), as well as the perspectives for future scientific and professional development. The thesis includes four main parts.

The first part is devoted to the analysis of the *main directions of research* pursued to date, indicating the original results obtained in personal studies. The objectives of my personal studies during doctoral and post-doctoral studies (after 2003) are selected from the ones recommended in national and international programs (e.g. P2 – Increasing of Economical Romanian Economy through Research Development and Innovation, Horizon 2020): better understanding of the mechanisms involved in the pathogenesis of neurodegenerative diseases and senescence, identification of potential peripheral biomarkers useful in assessing the risk of developing certain pathologies, bioprospection and evaluation of the therapeutic, antiageing, discovery of drugs potentially useful in regenerative therapies and high biocompatibility implant materials.

I was able to reveal few interesting aspects of the involvement of oxidative stress in Alzheimer's disease. Red cell membrane stability against an oxidative challenge represented by H₂O₂ was found to be reduced in patients with Alzheimer's disease, when compared with controls, while other markers of redox status (e.g. TEAC- Trolox equivalent antioxidant Capacity of plasma) were unchanged (M Gilca et al. 2014). Taking into account that brain and erythrocytes have a similar susceptibility toward free radicals, we suggested that this erythrocyte membrane stability assay a potential peripheral marker of cerebral oxidative stress in Alzheimer's disease our study confirms the hypothesis that Alzheimer's disease is not only a brain disease but also a systemic one.

In another important study, we have found that the PON/HDL-cholesterol ratio is a more accurate marker of cardiovascular risk than HDL-cholesterol in patients treated with atypical antipsychotics (Marilena Gilca, Piri, et al. 2014). Personal results, corroborated with literature data, suggest that HDL-cholesterol may have a modest role in estimating cardiovascular risk, a role that diminishes with age.

Another important research direction was represented by identification of new innovative therapeutic strategies, especially useful in oxidative stress associated diseases. I performed an intensive documentation work in order to investigate the therapeutic potential of relatively recent discoveries (e.g. antiageing effect of caloric restriction, hormetins, β type estrogen receptors, extraoral taste receptors) (Gilca et al. 2013; Gilca & Dragos 2017; Gaman et al. 2011; Gilca et al. 2007), to discover other perspectives on the endogenous

microenvironment, which might contribute to the re-thinking and re-modeling of the modern pharmacological paradigm.

In the area of innovative therapeutic strategies, I have conducted several human clinical studies, which have revealed that the oxidative stress can be modulated by caloric restriction or phytoceutical interventions (Gîlcă, Soian, et al., 2003; Gîlcă, Chirilă, et al., 2003; Gîlcă et al., 2009). We have already showed that the short term total fasting (3 days) was a minor nitrogen stress (mirrored in the increase in nitrate + nitrite plasma levels), which induces a reorganization of antioxidant protection and a reduction in lipid peroxidation, reflected in a decrease in malondialdehyde levels. We suggest that practicing intermittent short-term fasting period could be beneficial for subjects with pathologies associated with oxidative stress, and intend to verify this hypothesis in future studies. The administration of Geriforte (a herbomineral food supplement) to healthy human subjects indicated a strong cytoprotective activity of Geriforte on erythrocytes under exposure to azo-bis-2-amidinopropane dihydrochloride (AAPH) (Gîlcă et al. 2009).

Another recent interest in my research in the area of innovative therapeutic strategies is the potential role of ethnopharmacology and traditional knowledge in data mining and bioprospection (Gilca & Barbulescu 2015). I have recently developed a new concept in pharmacognosy: *the phytomolecular taste* or the molecular taste of a medicinal plant. The *phytomolecular taste* was defined in a recent article published in the Journal of Ethnopharmacology (Dragos & Gilca 2018). It indicates all the tastes of the main tastants found in that medicinal plant. In order to understand the distribution of ethnopharmacological activities between plants, we have built PhytoMolecularTasteDB, a database that is an international premiere, which contains 431 medicinal plants, 94 ethnopharmacological activities, 223 chemical classes of phytochemicals and 438 plant derived tastants (tastants displaying all tastes plus phytochemicals capable of triggering trigeminal orosensing). Phytomolecular taste indicates all the tastes of the major tastants found in one medicinal plant.

After the statistical analysis in PhytoMolecularTasteDB we concluded that the phytomolecular taste is a predictor of the ethnopharmacological activities of the medicinal plant, while the chemical classes of the phytocomponents do not. We have also concluded in another study that the antioxidant capacity versus herbal pro-oxidative potential might be a potential tool in selection of medicinal plants in phytotherapy (Marilena Gilca, Gaman, et al. 2014).

Evaluation of Sevofluran regenerative potential in cardiac surgery (Munteanu et al. 2016) and characterization of new biomaterials containing plant extracts in view of their use

as implants (Floroian et al. 2016) are two other personal scientific interests, studied in collaboration with my colleagues from other departments or universities.

The second part includes my professional achievements. My postgraduate training materialised in a Master Degree in Biostatistics (2010), the PhD in Medicine. Details are given on my professional training acquired by participation in international governmental scholarships (in Denmark, Food Research Institute, Faculty of Veterinary Medicine, Copenhagen) and continued education short term courses. The author's professional training and development has been achieved so far in interdisciplinary teams, where I participated as either member of national or international projects or coordinator (1 national project, Viasan 426/2004: "Senescence – new perspectives on redox mechanisms and potential therapeutic implications").

The third part is devoted to my academic achievements. Since 1994 I have been a member of the academic staff at the Faculty of Medicine of Carol Davila University of Medicine and Pharmacy, Bucharest. My academic achievements include: multiple and interdisciplinary teaching activities (lectures in biochemistry, clinical biochemistry, phytotherapy, coordination of practical lessons of Biochemistry and Laboratory Techniques, Medicinal Plant Journal Club for students, etc.), writing numerous books and book chapters published by national or international publishers, participation in two popular educational POSDRU projects as long term expert, in which hundreds of students were enrolled, high number of Web of Science citations per paper (total of 233, an average of 15.53 per article), H index 6, and other scientific academic activities. The international recognition of my research activity was accomplished by the acceptance for publication of 17 scientific articles included in the ISI Web of Science Core Collection, to which I am the principal author or co-author (10 as principal author since the last promotion). I have also published 17 articles in journals indexed in international databases (BDI) of which 5 articles since the last promotion (2014) and 6 other articles in CNCSIS indexed journals. I obtained several national or international awards. I am also member in reviewer teams of journals ISI indexed or indexed in other international data bases, member in the organiser committees of two International Conferences (New Trends on Sensing-Monitoring-Telediagnosis for Life Sciences – NT SMT-LS 2017, NT SMT-LS 2018).

The fourth part includes the strategies envisaged for my future professional and scientific development, main research directions. A particular area of my future research will be to continue the studies initiated in recent years that are focus on oxidative stress and antioxidants. Few topics will be: evaluation of oxidative alterations of erythrocytes as

probable linker of Alzheimer's disease and diabetes, development of a personalized integrative approach to diabetes based on multi-factorial etiopathogenic assessment, conducting phytoceutical and nutraceutic interventions with redox modulator potential, elaborating innovative strategies for personalizing phytoceutical and nutraceutical interventions, developing new biomaterials with potential applications in the field of implants, testing the universal validity of PhytoMolecular taste concept and its practical applications. I have initiated a new collaboration with a partner in London on a topic of interest to this research group too.

I will work towards increasing the number of active young scientists (doctoral and undergraduate students) involved in research projects and for attaining excellence in our professional activities. It is my belief that supporting the creativity of young researchers (doctoral, master or undergraduate students) and maintaining our collaboration with high expertise colleagues from Romania and abroad is the key towards success, high scientific performance, innovation and great discoveries.

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Assoc. Prof. Marilena Gîlcă-Vasile, PhD, MD
Biochemistry
Department of Functional Sciences I
Faculty of Medicine
Carola Davila University of Medicine and Pharmacy
Bucharest, Romania

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